STATINS PREVENT ATRIAL FIBRILLATION AFTER CARDIAC SURGERY?

To the Editor:

In a systematic review by Liakopoulos and associates,[1] statin use was associated with a 22% reduction in the unadjusted odds for any type of atrial fibrillation (random effects pooled odds ratio [OR], 0.78; 95% confidence interval, 0.67–0.90; $P = .0010$). Assessment of publication bias using visual examination of the funnel plot, however, revealed asymmetry around the mean OR with smaller studies tending toward larger positive effects. Significant publication bias was indeed confirmed ($P = .0003$) using Egger's weighted regression analysis. To assess the effect of possible publication bias, we calculated the pooled OR adjusted for publication bias using the ''trim and fill'' algorithm.[2] The ''trim and fill'' is probably the most popular method for examining the possible effect of publication bias on the pooled estimate and can be defined as an iterative nonparametric adjustment method based on a rank-based data augmentation technique to account for asymmetry on the funnel plot. The estimated OR for 18 studies, including 5 ''missing'' studies (random effects pooled OR, 0.87; 95% confidence interval, 0.74–1.02), is substantially different from the original estimate without adjustment for missing studies (Figure 1). Therefore, preoperative statin therapy may not be associated with a reduction in the incidence of atrial fibrillation after cardiac surgery.

Meta-analyses are subject to bias because smaller or nonsignificant studies are less likely to be published, and most meta-analyses do not consider the effect of publication bias on their results.[3] A funnel plot is a simple scatter plot of the effect estimates from individual studies against some measure of each study's size or precision, and the plot should approximately resemble a symmetric (inverted) funnel

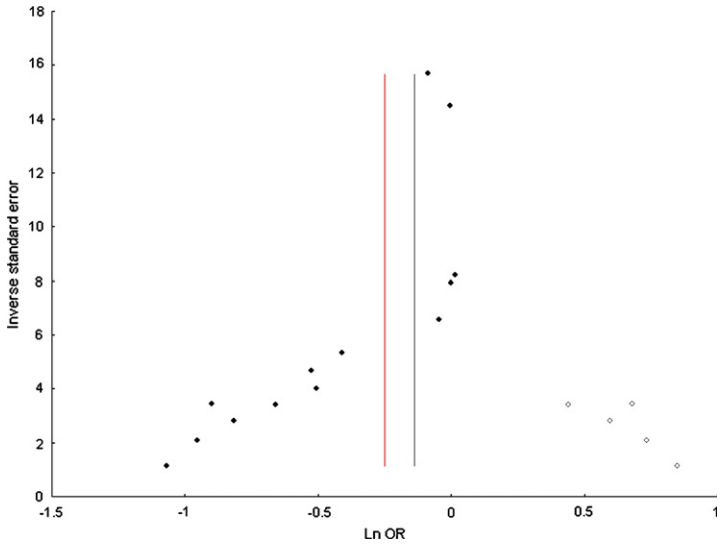

FIGURE 1. Funnel plot adjusted for publication bias. Published (*closed circles*) and missing (*open circles*) studies. Pooled point estimates with (*red vertical bar*) and without (*black vertical bar*) adjustment for publication bias. *OR*, Odds ratio.

in the absence of bias.[4] Although funnel plot asymmetry has long been equated with publication bias, the funnel plot should be seen as a generic means of displaying small study effects: a tendency for the effects estimated in smaller studies to differ from those estimated in larger studies.[5] Publication bias should be seen as one of a number of possible causes of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) and considered as only one of a number of possible explanations when there is evidence of small study effects.[4] In the present analysis, because there is evidence of significant funnel plot asymmetry (small study effects) by Egger's test, publication bias is considered as only one possible explanation. The ''trim and fill'' algorithm[2] requires no assumptions about the mechanism leading to publication bias and does not take into account reasons for funnel plot asymmetry other than publication bias.[4] Therefore, it is appropriate in the present analysis that we should correct for funnel plot asymmetry arising from publication bias using the ''trim and fill'' algorithm. If the conclusion of the meta-analysis remains unchanged after adjustment for the publication bias, the results can be considered reasonably robust, excluding publication bias. Researchers should check routinely whether conclusions of systematic reviews are robust to possible nonrandom selection mechanisms.[3]

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Reply to the Editor:

With great interest we read the comment by Takagi and colleagues[1] with regard to the analysis of publication bias in our previous report.[2] Our systematic review carefully assessed the presence of publication bias by Egger's weighted regression statistic and visual assessment of the funnel plot, tools that are generally recommended for assessment of publication bias. As correctly stated by the authors, both tests revealed evidence of substantial publication bias for any of the analyzed outcomes (any atrial fibrillation: $P = .0003$; new-onset atrial fibrillation: $P = .0001$), with visual examination of the asymmetric funnel blot underscoring a small study effect. Consequently, the results of our systematic review showing a 22% reduction in the unadjusted odds for any type of atrial fibrillation in patients with preoperative statin intake are extensively discussed in light of existing publication bias, as presented in the Discussion, Results, and Limitations sections of our article.

Nevertheless, we disagree with the authors' statements that advocate a deliberate use of the trim and fill method by Duval and Tweedie[2] for assessment of publication bias for several reasons. The basis of the method is to remove the smaller studies causing funnel plot asymmetry and to provide an estimated adjusted intervention effect based on the filled (ie, missing) studies. However, the trim and fill method is built on the assumption that there must be a symmetric funnel plot, which may not always be true. Second, it does not take into account the true mechanisms of publication bias or reasons for funnel plot asymmetry other than publication bias. Finally, the method is known to perform poorly in the presence of substantial heterogeneity among studies,[3,4] which was also present in our report. These are the reasons for not using the trim and fill method in our primary analysis. When taking the aforementioned restrictions into account, the ''recalculated'' odds ratio provided by Takagi and colleagues for the end point ''any atrial fibrillation'' should be interpreted cautiously and within the limitations of the trim and fill method, because there is no guarantee that the adjusted intervention effect would have been observed in the absence of publication bias.

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TREATMENT OF RECURRENT AORTIC PROSTHETIC DETACHMENT WITH MODIFIED BENTALL PROCEDURE

To the Editor:

I enjoyed the recent article ''The Treatment of Recurrent Aortic Prosthetic Detachment with Modified Bentall Procedure: Results of Two Cases.''[1] The authors described 2 cases of surgical management using a translocated Bentall procedure with a mechanical prosthesis. I have used a similar technique with a porcine or bovine prosthesis in patients with severe endocarditis in whom a valve homograft was not available. A second useful application is in the case of an aortic root that requires replacement and a bioprosthesis is the prosthesis of choice. The technique has the advantage of being more hemostatic because a rigid mechanical or bioprosthetic ring is not positioned on the native aortic annulus at the root. In the event of bleeding at the root, it is much easier to place a suture into the cuff of the conduit rather than the rigid aortic valve prosthesis resting on the annulus.

In addition, if the aortic valve requires replacement, it is easier to change the aortic valve than redo the aortic root replacement.

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Reply to the Editor:

We appreciate the comments by Dr Frank A. Baciewicz on our article, ''The Treatment of Recurrent Aortic Prosthetic Detachment with Modified Bentall Procedure: Results of Two Cases.'' His respectable clinical experiences briefly describe a similar technique with a bioprosthesis in patients with endocarditis or requirement of aortic root replacement and its advantages.